receiving a whole-cell vaccine (SolcoUrovas, Solco, Basel, Switzerland) containing heat-killed bacteria from 10 human uropathogenic strains, including six *Escherichia coli* strains and one strain each of *Proteus mirabilis*, *Proteus morganii, Enterococcus faecalis*, and *Klebsiella pneumoniae*, had a significant delay in acquiring their first reinfection compared with women who were given placebo. In the trial reported here, the goal was to extend the protection period beyond 8 weeks (first randomized, placebo-controlled trial) by use of booster suppositories. The investigators randomized 36 patients to intermittent vaginal suppository treatments of vaccine or placebo; one group received real vaccine for 14 weeks (vaccine-vaccine), one group received real vaccine for 2 weeks and then placebo (vaccine-placebo), and the third group received placebo for 14 weeks (placebo-placebo). There were no reinfections in 50% of the vaccine-vaccine group, 25% of the vaccine-placebo group, and 17% of the placebo-placebo group. In patients with reinfections, the median times to reinfection were 46, 21, and 16 days, respectively, in these three groups. There were no significant side effects of treatment. Vaginal immunization for recurrent UTIs may someday be a safe and effective treatment method.

Prevention of Recurrent Urinary Infections with Immuno-Active *E. coli* fractions: A Meta-Analysis of Five Placebo-Controlled, Double-Blind Studies

Bauer HW, Rahlfs VW, Lauener PA, Blessmann GS.
Int J Antimicrob Agents. 2002;19:451–456.

The authors performed a meta-analysis of five studies over the last decade to evaluate the effect of an oral vaccine (Uro-Vaxom, Sanofi Winthrop GmbH, Munich, Germany) developed from a bacterial extract consisting of 18 uropathogenic *Escherichia coli* strains. The efficacy of this oral vaccine has actually been investigated in 12 studies, but only five were placebo-controlled, randomized, double-blind studies. The primary criterion in all studies was the number of recurrences per patient. The studies evaluated were all basically the same: 3 months' treatment with observation and a further observation period of 3 months without treatment. A total of 717 patients were enrolled and randomized in the five studies; 501 were subsequently evaluable. There was a statistically significant decrease in recurrences in patients treated with the oral vaccine compared with placebo in every study. The pooled odds ratio (2.28) demonstrated at least statistical proof for a relevant drug effect, of modest size at least. The number of UTIs in patients treated with this vaccine was 0.15–0.82 per year, which compares favorably with low-dose antimicrobial prophylaxis. The safety and tolerability of the oral vaccine was good, with no real difference in minor side effects compared to placebo and no serious side effects reported. Oral immunotherapy with this or similar products may turn out to be effective therapy in the prevention of UTIs.

Conclusion

Recurrent UTIs in women are currently being treated with episodic, physician-directed therapy, low-dose prophylaxis, postcoital therapy, and patient self-directed therapy. All these approaches employ antibiotics and are subject to resistance problems, side effects, and cost considerations. Immunotherapy, with a vaginal or oral preparation, may turn out to be an effective alternative to antibiotics in the prevention of recurrent UTIs. ■

References

1. Nickel JC. Urinary Tract Infections in Adults. In: Teichman JMH, ed. *20 Common Problems in Urology*. New York, NY: McGraw-Hill; 2001:63–76.

Erectile Dysfunction

Prescribing PDE5 Inhibitors: Who Is the "Normal" Man?

Reviewed by Jacob Rajfer, MD
UCLA School of Medicine and Division of Urology, Harbor-UCLA Medical Center, Los Angeles, CA

[*Rev Urol.* 2002;4(4):197–198]

Sex, sex, sex! Men are imprinted to think about it all the time—not only when they are awake, but also when asleep. As men age and their erectile function changes for the worse—in some men as early as their 20s and noticeably in 40% of men by the time they reach age 40—nocturnal erections follow suit. Ever since the phosphodiesterase type 5 (PDE5) inhibitors were released for clinical use for the treatment of erectile dysfunction (ED) in 1998, the mantra has always been that these drugs should only be used in men with ED and not in "normal" men. The fear has always been that these drugs will be "abused" by normal men. How was "abuse" defined? It was defined as making erections last longer and decreasing the refractory time between ejaculations.

As clinical experience with the use of PDE5 inhibitors has been gained over the past 4 years, the following have become apparent in men with ED: 1) that PDE5 inhibitors are not only effective in improving erectile function, but

the drugs are relatively safe and free from any significant side effects; and 2) in addition to daytime erections, the drugs enhance nocturnal tumescence.[1] Well, what about the drug in normal men?

Effects of Sildenafil on Nocturnal Penile Tumescence and Rigidity in Normal Men: Randomized, Placebo-Controlled, Crossover Study

Rochira V, Granata AR, Balestrieri A, et al.

J Androl. 2002;23:566–571.

In 2000, Aversa and colleagues from Italy showed that the refractory time can be decreased in normal men who take sildenafil.[2] In another, elegant study by Rochira and colleagues from Italy, 44 normal men (who supposedly did not have ED) were given sildenafil (50 mg) and/or placebo in a randomized, placebo-controlled, crossover study, and nocturnal penile erections (NPT) were monitored. The authors concluded from their observations that sildenafil was effective in improving NPT in normal men, and some of the normal men recognized this effect up to 9 hours post-administration.

Does this mean that these drugs should be prescribed in "normal men" who request them? Let us think about this for a moment. Why would a man want to have a decreased refractory time—in other words, why would he want to decrease the time between coitus episodes? I assume that it would be because he had been able to at one time in his life and is now unable to do so as he ages. If we accept this premise, that the patient has recognized a change over time, then the "normal men" who we recruit into such studies as are described above should ideally be in their 20s, not close to 40 years of age as was the age group (40 ± 13 years) for the Rochira study. It is my assumption that the reason a man who is in his 20s, 30s, or whatever age requests something to improve his sexual function is because he has noticed a change from his "younger" days. And because 40% of the men in the Massachusetts Male Aging Study had some form of ED by age 40, I assume that many of Rochira's subjects, though "normal" according to questionnaire data, were different physiologically from their "youth," and that is why the sildenafil improved the outcome parameters that were used in this study.

What we need in the literature is a study of "normal" men in their 20s who are at the pinnacle of their sexual prowess. My belief at this time is that if such a study were performed, there would be very little significant change in erectile function and ejaculatory refractoriness in truly normal men who are administered a PDE5 inhibitor such as sildenafil.

It is for the aforementioned reasons and because of the proven safety of this class of drugs that I have very little concern in prescribing it to men at any age, if they provide me with enough evidence on the history that a change has occurred in their erectile function. ■

References

1. Montorsi F, Maga T, Strambi LE, et al. Sildenafil taken at bedtime significantly increases nocturnal erections: results of a placebo-controlled study. *Urology.* 2002;56:906–911.
2. Aversa A, Mazzili F, Rossi T, et al. Effects of sildenafil (Viagra) administration on seminal parameters and post-ejaculatory refractory time in normal males. *Hum Reprod.* 2000;15:131–134.

Prostate Cancer

Evolving Role of Pro-PSA as a New Serum Marker for the Early Detection of Prostate Cancer

Reviewed by Masood A. Khan, MD, Alan W. Partin, MD, PhD

Department of Urology, Johns Hopkins University Hospital School of Medicine, Baltimore, MD

[*Rev Urol.* 2002;4(4):198–200]

The development and subsequent routine use of prostate-specific antigen (PSA) over the past decade has revolutionized the management of prostate cancer. PSA has increased our ability to detect and, in turn, treat early prostate cancer; however, the major drawback of PSA is its relative lack of specificity. This is especially important in the critical diagnostic range of 4–10 ng/mL, where an elevated PSA may reflect either prostate cancer or benign disease, such as benign prostatic hyperplasia (BPH). This lack of specificity has led to unnecessary prostate biopsies, with associated anxiety, cost, and potential morbidity.

It was discovered in 1991 that serum contains two distinct major forms of PSA: one form is covalently bound to endogenous serum protease inhibitors like α_1-antichymotrypsin and is known as *complexed PSA*; the other form is present in a "free," nonactive, noncomplexed form and is known as *free PSA*.[1,2] The measurement of the ratio of free to total PSA has led to a modest but significant improvement in the discrimination of prostate cancer from BPH in men with PSA levels between 4.0 and 10.0 ng/mL. This is attributable to the association of BPH with high levels of free PSA, compared with prostate cancer.[3] The free PSA form is a heterogeneous group consisting of at least three different subforms of inactive PSA. One form has